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# Review on Schizophrenia

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**ABSTRACT**

Today, schizophrenia affects approximately 1% of people worldwide and is a persistent, often devastating mental illness. The etiology of schizophrenia is still unknown despite a century of research. Despite the fact that medications, particularly pharmaceutical ones, have been used extensively for almost 50 years, there is little proof that they have significantly benefited the lives of the majority of schizophrenia sufferers. As we treat schizophrenia as a neurodevelopmental disorder and consider psychosis a late, potentially avoidable stage of the illness, these currently dismal outcomes may shift. In contrast to how we have seen this condition for the previous century, this "rethinking" of schizophrenia as a neurodevelopmental disorder offers new hope for prevention and a treatment over the next 20 years.

## INTRODUCTION

The role of neurotrophins and their precursor, pro-neurotrophins, in the pathophysiology of several CNS disorders, including depression and schizophrenia, is gaining attention due to recent genetic, neurochemical, and therapeutic research (Angelucci et al., 2005a, Angelucci et al., 2005b, Durany and Thome, 2004, Shoval and Weizman, 2005, Tapia-Arancibia et al., 2004). In the central and peripheral nervous systems, neurotrophins support the development, differentiation, and survival of neuronal cells under stressful conditions (Sofroniew et al., 2001). Brief chemical summaries, regulatory mechanisms of mature and pro-neurotrophin expression and distribution, and their opposing functional roles through differential neural membrane receptor-mediated signaling mechanisms will all be covered in this review (Arévalo and Wu, 2006, Huang and Reichardt, 2003, Schor, 2005, Teng). Additionally, This review will also concentrate on the role neurotrophins play in schizophrenia.[1]

Although the fundamental structures of all neurotrophins are similar, their varied domains dictate how each one binds to its particular receptor to produce different biological effects (Huang and Reichardt, 2003). The receptors on the cell surface fall into two groups. Tropomyosine-related kinase (Trk) receptors are high-affinity protein kinase receptors that neurotrophins specifically interact with (Huang and Reichardt, 2003). NGF binds to TrkA to promote biological effects; TrkB mediates BDNF and NT-4 bindings; TrkC primarily mediates NT-3 bindings (Fig. 1). Moreover, p75NTR, a member of the tumor necrosis factor (TNF) receptor superfamily, is another neurotrophin receptor with which all neurotrophins can interact with low affinity. Due to its lack of intrinsic enzymatic activity, P75NTR communicates via a variety of protein-protein interactions that are facilitated by its death and intracellular juxta-membrane domains. Fascinatingly, it has been observed that there is cross-talk between Trk receptors and other membrane receptors, including p75NTR (which was previously covered), G-protein-coupled receptors, vannilloid receptors, c-ret receptors, and Na+ and Ca++ ion channels, all of which support the biological responses mediated by neurotrophins (Huang and Reichardt, 2003). According to Bramham and Messaoudi (2005), BDNF can improve long-term potentiation, long-term depression, and some types of short-term synaptic plasticity, possibly through its TrkB receptor. Furthermore, learning and memory—particularly spatial memory—are known to be facilitated by BDNF and TrkB (Mu et al., 1999).[2]

## PATHOPHYSIOLOGY

Neurotransmission abnormalities have served as the foundation for theories on the etiology of schizophrenia. The majority of these hypotheses revolve around either an overabundance or a shortage of neurotransmitters, such as glutamate, serotonin, and dopamine. Other ideas link the neurochemical imbalance associated with schizophrenia to aspartate, glycine, and gamma-aminobutyric acid (GABA).[3]

Many of the symptoms linked with schizophrenia are thought to be related to abnormal activity at dopamine receptor sites, notably D2. There are four identified dopaminergic pathways . The caudate nucleus is where the nigrostriatal pathway finishes after emerging from the substantia nigra. It is believed that the extrapyramidal system is impacted by low dopamine levels along this route, which results in motor symptoms. In the presence of extra dopamine, the mesolimbic pathway—which runs from the ventral tegmental area (VTA) to limbic areas—may contribute to the positive symptoms of schizophrenia.

The VTA and the cortex are connected by the mesocortical circuit. [4]In schizophrenia, reduced mesocortical dopamine levels are assumed to be the cause of negative symptoms and cognitive difficulties. The pituitary gland receives input from the hypothalamus via the tuberoinfundibular route. Reduced libido, ammenorrhea, galactorrhea, and increased prolactin levels are caused by a reduction in tuberoinfundibular dopamine or its blockage. The finding that lysergic acid diethylamide (LSD) amplified the effects of serotonin in the brain gave rise to the serotonin hypothesis on the onset of schizophrenia. Unlike prior drugs that solely targeted dopamine receptors, subsequent research led to the discovery of pharmacological molecules that blocked both serotonin and dopamine receptors.[5] It was discovered that the more recent substances were useful in reducing both the positive and negative symptoms of schizophrenia.[6] Glutamate is the primary excitatory neurotransmitter in the brain, and its activity is the subject of another theory regarding the symptoms of schizophrenia.[7] This notion developed in reaction to the discovery that two noncompetitive NMDA/glutamate antagonists that cause symptoms similar to schizophrenia are phenylciclidine and ketamine.Six Thus, it was feasible to explain why people with schizophrenia display negative, emotional, and cognitive symptoms by pointing out that NMDA receptors are inactive in the normal control of mesocortical dopamine neurons.[8]

Schizophrenia patients seem to experience observable physical alterations in their brain tissue. For example, those who are at a higher risk of experiencing a schizophrenia episode had smaller medial temporal lobes in addition to larger third and lateral ventricles.[9]

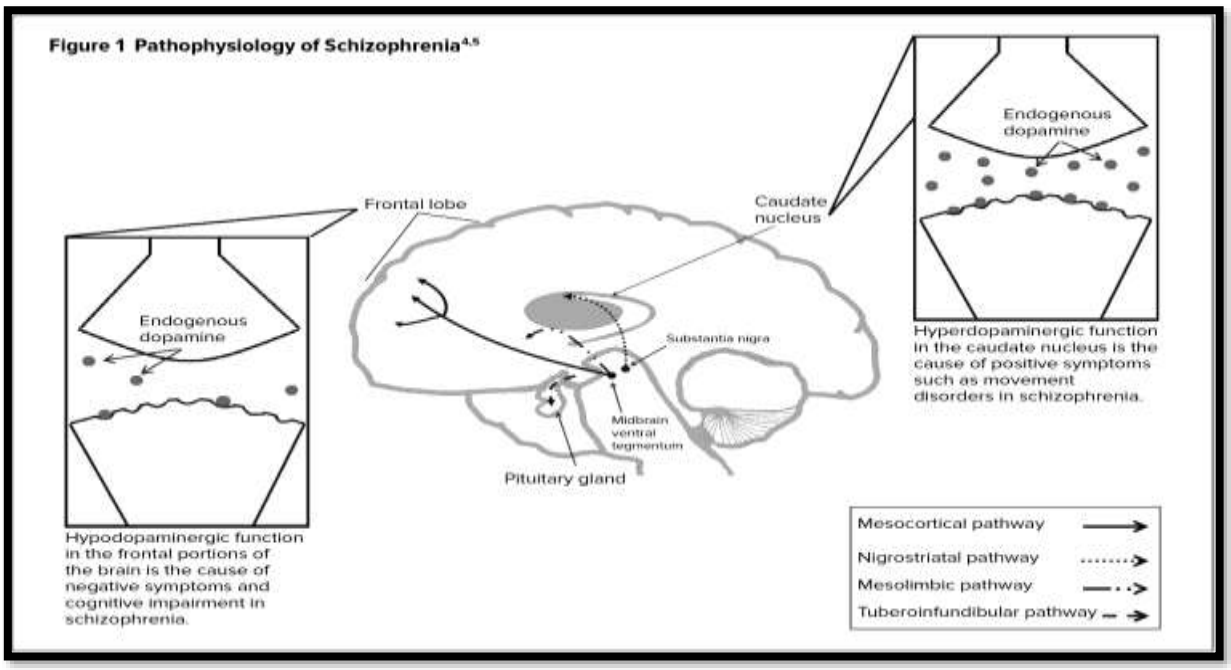


**Fig. PATHOPHYSIOLOGY OF SCHIZOPHRENIA**

## RISK FACTORS OF SCHIZOPHRENIA

### 1.GENETIC RISK

While environmental risk factors are the primary focus of this research, genetic risk also plays a role [10]. Two big twin studies conducted recently have improved our knowledge of the latter's nature. A population-based sample of twins with clinically diagnosed schizophrenia from Finland was studied by Cannon et al. [11], who found that additive genetic factors accounted for around 80% of the variance in schizophrenia liability. Using operational definitions of schizophrenia, a publication from the Maudsley Twin Register in London yielded very comparable results [12]. Cardno et al. questioned whether there is a unique vulnerability to schizophrenia as part of the same Maudsley investigation. The results showed that mania and schizophrenia are prone to both common and diagnosis-specific genetic effects. In fact, it could be more fair to consider the genes that determine continuous variation in the dimensions of symptoms such as positive, negative, manic, and depressed symptoms rather than the genes that specifically cause schizophrenia.[13]

### 2.PLACE AND TIME OF BIRTH

Numerous studies [14] suggest that living in a city at birth or growing up increases one's risk of developing schizophrenia. One of the most remarkable was conducted by Mortensen et al. [15], who examined the impact of birth season, geography, and family history on the risk of schizophrenia in a sizable Danish population. They found that the relative risk of schizophrenia was 1.11 for late winter birth and 2.40 for urban birth. This study also demonstrated that there is a dose-response relationship for urban birth, meaning that the risk increases with the size of the birth town. This implies a causal relationship. Mortensen et al. noted that a comparatively minor increase in risk will result in a substantial rise in the number of persons living in and born in cities. In fact, they found that the population attributable risk (PAF) for being born in an urban area was 34.6%, while the corresponding rates for having a mother or father with schizophrenia were 9% and 7%. Therefore, the impact of being born in an urban area was significantly greater than the impact of having a relative.[16]

**3.PREGNANCY AND BIRTH COMPLICATIONS**

Numerous studies have found an excess of obstetric complications (OCs) among people who go on to develop schizophrenia; however, the majority of these studies were too small to determine which patients were most likely to have been exposed and which difficulties are specifically linked to schizophrenia. Verdoux et al. [17] conducted a meta-analysis to address this, combining data from 11 distinct study groups that employed the Lewis-Murray scale.

In schizophrenia cases with onsets younger than 22 years old, an excess of OCs was discovered in the past. This result has been confirmed multiple times, most recently by Rosso et al. , who demonstrated that OCs linked to hypoxia markedly elevated the risk of early-onset schizophrenia but not late-onset schizophrenia.[18]

**4.STRUCTURAL BRAIN ABNORMALITY**

Schizophrenia has been linked to structural brain abnormalities in numerous magnetic resonance imaging (MRI) investigations; however, the majority of these research are small case-control studies [19]. Everyone agrees that individuals with schizophrenia and, to a lesser degree, affective psychosis have larger mean lateral ventricles [20]. According to Jones et al. , there is a linear trend in the relationship between the size of the lateral ventricle and the chance of developing schizophrenia. Large ventricles do not appear to belong to any subgroup; rather, ventricular enlargement is better understood as a persistent risk factor.[21]

## TREATMENT OPTIONS

**1. Nonpharmacological Therapy**

Targeting symptoms, averting relapse, and enhancing adaptive functioning are the main objectives of treating schizophrenia in order to help the patient reintegrate into society. To maximize long-term results, both nonpharmacological and pharmacological treatments must be used, as patients seldom regain their baseline level of adaptive functioning. The cornerstone of managing schizophrenia is pharmacotherapy, yet lingering symptoms could still exist. Psychotherapy and other nonpharmacological treatments are crucial because of this[23]. Three categories can be used to categorize psychotherapeutic approaches: group, individual, and cognitive behavioral. The field of psychotherapy is one that is always changing. Narrative therapy, mindfulness therapy, and meta-cognitive training are examples of emerging psychotherapies .It is best to employ nonpharmacological therapy in conjunction with pharmaceuticals rather than as a replacement for them[24].

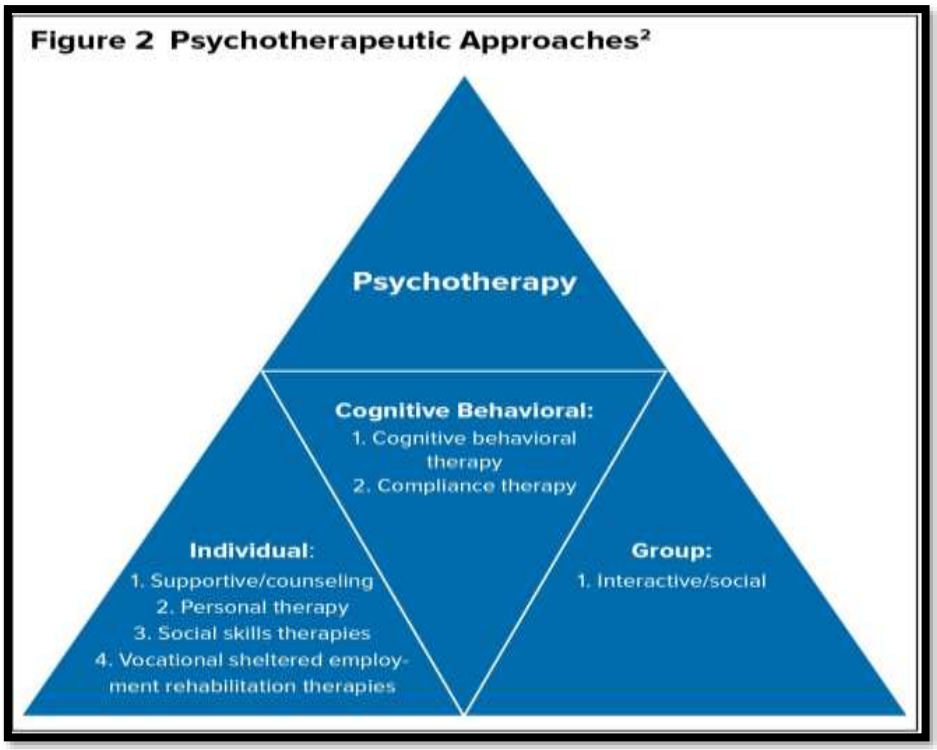


**Fig. PSYCHOTHERAPEUTIC APPROACHES**.

Nonpharmacological therapy can also help to guarantee that patients continue taking their drugs as prescribed. They not only cover gaps in pharmacological treatments. Depending on the study, nonadherence rates in schizophrenia might range from 37% to 74%.19 For a variety of reasons, people with mental illnesses typically have lower adherence rates. They might have grandiose symptoms or paranoia; they might deny their condition; they might have negative affects that discourage them from taking more medication; or they might not realize they need it. Individuals with schizophrenia

who discontinue taking their medication run the risk of experiencing a relapse, which may require hospitalization. As a result, it's critical to inform patients about their illness, treatment risks, and efficacy.[25] Several psychotherapies, such as cognitive behavioral therapy (CBT), personal therapy, and compliance therapy, can assist in educating patients about the significance of medication compliance. Treatment plans that include family support have been demonstrated to enhance social functioning and reduce rehospitalization in addition to concentrating on the patient. Family members might be trained how to keep an eye on their loved one and when to notify the doctor about side effects. Family engagement is promoted by most psychotherapies.[26]

**2. Pharmacological Therapy**

Without antipsychotic medications, it is challenging to carry out successful rehabilitation programs for the majority of schizophrenia patients. As the majority of illness-related alterations in the brain take place within five years following the initial acute episode, it is imperative that medication treatment be started as soon as possible.[27] A worse prognosis is predicted by alcohol and drug misuse, as well as illegal use of stimulants to the central nervous system, such as amphetamines[28]. Drug interactions can also result from the use of alcohol, caffeine, and nicotine.[29]When a patient experiences an acute psychotic episode, medication therapy should be started right once. The aim of the first seven days of treatment is to reduce the level of antagonism and try to get the patient back to sleeping and eating normally.[30] The right dosage should be titrated at the beginning of treatment in accordance with the patient's response. After the acute phase of treatment for schizophrenia, maintenance therapy should be administered with the goal of enhancing socialization, mood, and self-care. To assist stop relapses, maintenance therapy is required. In patients getting maintenance medication, the incidence of relapse is 18% to 32% against 60% to 80%, respectively, in individuals not receiving such therapy. Following the remission of the initial psychotic episode, medication therapy ought to be maintained for a minimum of 12 months.[31]

## CONCLUSION

With a multifaceted etiology, schizophrenia presents with a complicated presentation. However, developments in neuroscience have revealed roles for important circuits in the development of positive, negative, and cognitive symptoms, particularly involving frontal, temporal, and mesostriatal brain areas. The mechanism by which the current pharmaceutical treatments work—blockade of the dopamine D2 receptor—contributes to its side effects. Nonetheless, the circuit processes that are covered in this article point to new therapy targets that could be especially helpful in symptom domains that are poorly treated by current drug

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